REMARKS

Claims 11-18 have been replaced with new claims 19-22. Support for the new claims can be found throughout the specification. More specifically, support for new claim 19 can be found on page 2, first four paragraphs; the paragraph bridging pages 4-5; and in the Examples starting on page 12 of the specification.

Priority

Applicants acknowledge the priority documents have been received.

Claim Objection

Claim 12 has been canceled. Therefore, Applicants respectfully request this objection be withdrawn.

35 U.S.C. 112, first paragraph rejection

Claims 11-18 were rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for "treatment of angiongenesis", "inhibiting basic fiberblast growth factor induced angiogenesis" or "inhibiting angiogenesis". According to the Examiner, the specification does not enable one skilled in the art to which it pertain, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicants have replaced claims 11-18 with new claims 19-22. These claims relate to methods of treating a patient suffering from a proliferative disease comprising administering an effective amount of a bisphosphonate wherein the bisphosphonate acts to reduce angiogenesis. The proliferative disease is define as a disease selected from rheumatoid arthritis, osteoarthritis, breast cancer, colon cancer, small cell lung cancer, prostate cancer, diabetic retinopathy, psoriasis, haemangioblastoma or haemangioma. The bisphosphonates are defined as 3-amino-1-hydroxypropane-1,1-diphosphonic acid; 3-(N,N-dimethylamino)-1-hydroxypropane-1,1--diphosphonic acid; 1-hydroxy-ethidene-bisphosphonic acid; 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid; 3-(N-methyl--N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid); 1-(4-chlorophenylthio)methane-1,1-diphosphonic acid (tiludronic acid); 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid; 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosphonic acid; 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester; 1-hydroxy-2-

(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid; and 1,1-dichloromethane-1,1-diphosphonic acid.

It is believed the present set of claims are free from any 35 U.S.C. 112, first paragraph rejections because the claims do not define "treatment of angiongenesis", "inhibiting basic fiberblast growth factor induced angiogenesis" or "inhibiting angiogenesis". Furthermore, the indications are defined as rheumatoid arthritis, osteoarthritis, breast cancer, colon cancer, small cell lung cancer, prostate cancer, diabetic retinopathy, psoriasis, haemangioblastoma, haemangioma are supported by the Examples in the specification. Therefore, Applicants respectfully request that this rejection be withdrawn from consideration.

35 U.S.C. 102(b) and (e) Rejections

Claim 16 was rejected under 35 U.S.C. 102(b) as being anticipated by Katdare (WO95/29679) and claims 16-17 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,048,861. Claims 16 and 17 have been canceled and therefore Applicants argue that the 35 U.S.C. 102(b) and (e) rejections be withdrawn.

Applicants argue that none of the references cited teach each and every element as set forth in the present set of claims are found, either expressly or inherently, " *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). More specifically, none of the references cited teach methods of treating a patient suffering from a proliferative disease comprising administering an effective amount of a bisphosphonate wherein the bisphosphonate acts to reduce angiogenesis and is selected from the following compounds 3-amino-1-hydroxypropane-1,1-diphosphonic acid; 3-(N,N-dimethylamino)-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-ethidene-bisphosphonic acid; 1-hydroxy-3-(methylpentylamino)-propylidene-bisphosphonic acid; 6-amino-1-hydroxyhexane-1,1-diphosphonic acid; 3-(N-methyl--N-n-pentylamino)-1-hydroxypropane-1,1-diphosphonic acid; 1-hydroxy-2-(imidazol-1-yl)ethane-1,1-diphosphonic acid; 1-hydroxy-2-(3-pyridyl)ethane-1,1-diphosphonic acid (risedronic acid); 1-(4-chlorophenylthio)methane-1,1-diphosphonic acid (tiludronic acid); 1-hydroxy-3-(pyrrolidin-1-yl)propane-1,1-diphosphonic acid; 1-(N-phenylaminothiocarbonyl)methane-1,1-diphosphonic acid; 5-benzoyl-3,4-dihydro-2H-pyrazole-3,3-diphosphonic acid tetraethyl ester; 1-hydroxy-2-(imidazo[1,2-a]pyridin-3-yl)ethane-1,1-diphosphonic acid; and 1,1-dichloromethane-1,1-diphosphonic acid and wherein the proliferative disease is selected from rheumatoid arthritis, osteoarthritis, breast cancer, colon cancer, small cell lung cancer, prostate cancer, diabetic retinopathy, psoriasis, haemangioblastoma and haemangioma.

WO 95/29679 concerns a wet granulation formulation for bisphosphonic acids. Pharmaceutical applications are listed on page 10 of this application and only concern the therapeutic or prophylactic treatment of disorders in calcium or phosphate metabolism and associated diseases. Arthritis is mentioned as one of these diseases, but not osteoarthritis. That the reduction in bone resorption can alleviate the pain associated with osteolytic lesions and reduce the incidents and a growth said lesions is also mentioned. Not mentioned, however, is a treatment of any of the diseases as specified in claim 19 with a bisphosphonate, wherein the bisphosphonate acts as an angiogenesis inhibiting or reversing agent. Among the bisphosphonates mentioned in document WO 95/29679 figure: alendronic acid, olpadronate, ibandronate, and risedronate. As document WO 95/29679 does not disclose the method of treating a patient suffering from a proliferative disease comprising administering an effective amount of a bisphosphonate wherein the bisphosphonate acts to reduce angiogenesis as specified in independent claim 19, the document cannot take away novelty from the present set of claims.

35 U.S.C. 103(a) Rejection

Claims 11-15 were rejected under 35 U.S.C. 103(a) as being unpatentable over Askew et al. (U.S. Patent No. 6,048, 861).

Applicants request clarification from the Examiner with respect to which claims are rejected under 35 U.S.C. 103(a) as being unpatentable over Askew et al. (U.S. Patent No. 6,048,861) and further in view of Reszka et al. (U.S. Patent No. 6,416,964 B2).

With respect to Askew et al., the Examiner refers to the arguments set forth under the 35 U.S.C. 102(e) rejection as supporting the obviousness rejection, which states on page 9, first full paragraph:

> Askew teaches the use of composition comprising integrin receptor antagonist, bisphosphonates (e.g. alendronate, pamidronate, etc...) and a vascular endothelial growth factor inhibitor for the treatment, prevention or inhibition of angiogenesis, macular degeneration, inflammation, diabetic retinopathy, atherosclerosis and tumor growth (Abstract, column 34, lines 27-31 and claim 26).

The present set of claims do not describe the combination of a bisphosphonate and a vascular endothelial growth factor inhibitor for the treatment, prevention or inhibition of angiogenesis, macular degeneration, inflammation, diabetic, retinopathy, atherosclerosis and tumor growth.

Askew et al. (U.S. Patent No. 6,048,861) relates to compounds that are antagonists of the integrin receptors $\alpha v\beta 3$, $\alpha v\beta 5$ and/or $\alpha v\beta 6$ which are useful for inhibiting bone resportion. The

examples of organic bisphosphonates include alendronate, etidronate, pamidronate, risedronate, ibandronate and pharmaceutically acceptable salts thereof, please refer to column 34, lns. 27-30.

Applicants provide the following general comments regarding U.S. Patent No. 6,416,964. U.S. Patent No. 6,416,964 relates to methods of identifying modulators of kinases responsive to stress (title). The application describes bisphosphonates claimed to be useful for treating or preventing diseases or conditions that are mediated by, for example, abnormal bone resorption or angiogenesis. The diseases mentioned in this context are: osteoporosis, inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, arteriosclerosis, inflammation, and tumour growth. Myocardial ischemia, osteoarthritis, psoriasis, haemangioblastoma, haemangioma and pain are not mentioned in this document. The document mentions the following bisphosphonates: pamidronate, olpadronate, alendronate, etidronate, ibandronate, neridronate, BM210955, risedronate, tiludronate and clodronate and/or the respective acids.

U.S. Patent No. 6,416,964 in other words does not teach or suggest the methods of treatment of any of the diseases mentioned in independent claim 19, wherein the bisphosphonate acts to reduce angiogenesis. The document does not contain any hints that other diseases than the ones mentioned therein could be treated with bisphosphonates.

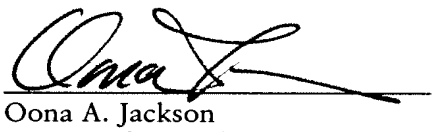
Based on the above arguments, Applicants respectfully request that the 35 U.S.C. 103(a) rejections be withdrawn from consideration.

Obviousness-Type Double Patenting Rejection

Claims 11-16 were rejected provisionally under the judicially created doctrine of double patenting over claims 9-10 of copending Application No. 10/484,482. Upon allowance of the claims, Applicants will file a Terminal Disclaimer.

Entry of this Response is respectfully requested.

Respectfully submitted,



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